

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 05: Depression and Other Mental Health Disorders

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www.ahrq.gov

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Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Yen-pin Chiang, Ph.D.
Acting Director
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Contents

Executive Summary	ES-1
Background	ES-1
Methods	ES-1
Results	ES-2
Discussion	ES-2
Depression and Other Mental Health Disorder Interventions	1
Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder	2
Off-Label Scopolamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder	6
Video Game for Cognitive Behavior Therapy for Adolescents with Major Depressive Disorder	9
References	12

Figures

Figure 1. Overall high-impact potential: off-label ketamine for treatment-resistant bipolar depression and major depressive disorder	4
Figure 2. Overall high-impact potential: off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder	7
Figure 3. Overall high-impact potential: video game for cognitive behavior therapy for adolescents with major depressive disorder	10

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the five topics for which (1) preliminary phase III data for drugs were available or programs were being piloted; (2) information was compiled and sent for expert comment before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Eighteen topics in this priority area were being tracked in the system as of May 15, 2014.) We present summaries of three topics (indicated below by an asterisk) that emerged as having some potential for higher impact on the basis of expert comments. We also describe the topics in this priority area that were included in the previous high impact report, but subsequently archived, and the two topics that were eligible for this high impact report but not deemed to have potential for high impact at this time. Topics in this Executive Summary and report are organized alphabetically. Readers are encouraged to read the detailed information that follows the Executive Summary.

Priority Area 05: Depression and Other Mental Health Disorders

Topic	High-Impact Potential
1. Lisdexamfetamine (Vyvanse) for treatment of binge-eating disorder	No high-impact potential at this time
2. *Off-label ketamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
3. *Off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder	Lower end of the high-impact-potential range
4. *Video game for cognitive behavior therapy for adolescents with major depressive disorder	Lower end of the high-impact-potential range
5. Vortioxetine (Brintellix) for treatment of major depressive disorder	No high-impact potential at this time

Discussion

A common focus among many interventions in development for mental health disorders is the search for alternative options addressing patients who have treatment-resistant forms of bipolar depression (BPD), major depressive disorder (MDD), and posttraumatic stress disorder. The underlying causes of these disorders are still being investigated but are understood to potentially involve abnormal modulation of one or more neurotransmitters, pathways, or receptors in the brain.

Presented with this challenge, investigators are examining a variety of treatment approaches, including new and derivative medications, nontraditional external therapeutic tools, and immersive cognitive behavior therapies.

Prior High-Impact Topics Archived Since December 2013 Report

The following two high-impact potential topics from the December 2013 report have been archived:

- **Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression:** Mifepristone is a cortisol antagonist and previously received FDA approval for treating symptoms of endogenous Cushing's syndrome. It is an abortifacient drug used to terminate early-stage pregnancies, and one of its manufacturers, Corcept Therapeutics, Inc. (Menlo Park, CA), was investigating it for rebranded use in treating psychotic major depression. However, in May 2014, Corcept halted development of mifepristone for this indication, citing a failure to meet primary endpoints in its phase III trial.
- **Deep brain stimulation (Reclaim DBS Therapy or Libra DBS) for treatment-resistant depression:** We previously tracked two deep brain stimulation (DBS) systems being investigated as interventions for treatment-resistant depression; in the December 2013 High-Impact report, these devices were discussed as a combined topic. The Reclaim[®] device (also marketed as Activa[®]) is manufactured by Medtronic, Inc. (Minneapolis, MN); Medtronic has since abandoned clinical trials for this indication but has stated that it will support independent researchers using the product in similar trials. We continue to track Libra[®], a DBS system manufactured by St. Jude Medical, Inc. (St. Paul, MN), that targets the subcallosal cingulate gyrus brain region for treating MDD. In April 2014, investigators from Emory University published preliminary clinical trial results demonstrating potential white matter cerebral biomarkers correlating with positive patient response to Libra DBS treatment.

Eligible Topics Not Deemed High Impact

- **Lisdexamfetamine (Vyvanse) for treatment of binge-eating disorder:** Lisdexamfetamine is a prodrug of dextroamphetamine, and FDA has approved it for treating attention-deficit/hyperactivity disorder. Lisdexamfetamine's manufacturer, Shire, plc (Dublin, Ireland), is pursuing an expanded indication for treating binge-eating disorder, which was recognized in the latest Diagnostic and Statistical Manual of Mental Disorders as a separate eating disorder. Although Shire has reported some positive results from phase III clinical trials, experts commenting on this intervention concluded that it has no high-impact potential at this time, citing three reasons: limited efficacy data for treating binge-eating disorder, failure to demonstrate superiority over behavior therapy, and high potential for abuse.
- **Vortioxetine (Brintellix) for treatment of major depressive disorder:** Vortioxetine is an atypical antidepressant with broad serotonin antagonist, agonist, and transporter inhibitor properties. In September 2013, the manufacturers, Takeda Pharmaceutical Co., Ltd. (Osaka, Japan), and H. Lundbeck a/s (Valby, Denmark), received FDA approval to market the drug for treating MDD. However, experts evaluating this intervention determined that it had no high-impact potential; instead, they considered it to represent little to no incremental improvement for treating MDD, citing clinical trial data that failed to show superiority over other available treatment options.

In the following sections we discuss three interventions for BPD and MDD. The first two interventions, off-label uses of ketamine and scopolamine, attempt to repurpose drugs approved by the U.S. Food and Drug Administration (FDA). These drugs' rapid antidepressant effects may make them particularly effective in treating both medically-refractory disease that has failed to successfully respond to two or more antidepressant medications and patients with severe depression, who have increased risks of suicidal ideation. The third intervention is a novel treatment for early-onset MDD, integrating cognitive behavior therapy into a role-playing video game, designed to appeal to adolescent patients. Preliminary data for these interventions are promising, and ongoing trials are clarifying the safety and efficacy of each treatment.

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts:** Although multiple FDA-approved medications are available, many patients in whom BPD or MDD has been diagnosed are not successfully treated using prescribed medications; therapeutic responses range from delayed to wholly inadequate. In these cases, patients are exposed to prolonged and increased risk of suicide and death. Ketamine (racemic ketamine hydrochloride), FDA-approved since 1996 as a general anesthetic, is being investigated for cases of treatment-resistant BPD and MDD with research being sponsored by multiple groups, including the National Institute of Mental Health (Bethesda, MD). Researchers hypothesize that ketamine's antidepressant properties are likely due to its role as a nonselective, high-affinity N-methyl-D-aspartate receptor antagonist; however, recent animal model studies have also revealed that ketamine's antidepressant effects may be mediated by regulation of mitogen-activated protein kinase (MAPK) signaling pathways.

In clinical trials, ketamine is most often administered as a single intravenous infusion. Preliminary data suggests that this dose produces rapid (within 2 hours) and relatively sustained (about 1–2 weeks long), significant reductions in depression symptoms, as measured by standard depression instruments. In small studies, ketamine administration also reduced suicidal ideation in depressed patients admitted to emergency departments. Most ongoing clinical trials are investigating optimal doses and regimens of ketamine, off-label, for specific patient populations; however, one manufacturer is studying esketamine, a purified enantiomer form of ketamine, for this indication.

Ketamine is a relatively inexpensive, but is classified as a Schedule III drug by the U.S. Drug Enforcement Administration and requires a license and prescription to obtain, which could affect diffusion for this indication. Off-label use may be further limited by the drug's unpredictable psychiatric side effects in some patients, including hallucinations, anxiety, and insomnia. Some clinical practices report offering ketamine infusions for treating depression and the amount they charge; patient blogs also report patient experiences and out-of-pocket costs of ketamine infusions for MDD. Reported fees ranged from \$525 to \$1,250 per infusion; patients reported that an intranasal formulation was much less costly. A September 2013 article in *Scientific American* on use of off-label ketamine for MDD reported that off-label prescribing of the drug has been increasing at a grass-roots level. Third-party payers do not pay for this use; thus, patients are paying out of pocket.

- **Key Expert Comments:** Experts commenting on ketamine for this indication were optimistic about its potential as a rapid-onset, effective treatment for BPD and MDD. They also stated that although ketamine could have a positive impact on patient health outcomes, it may shift patient care setting from oral self-administered therapy to physician's offices and infusion clinics. Some experts' enthusiasm for this intervention was tempered by the

limited and sometimes mixed clinical trial results, as well as safety risks of using a controlled substance.

- **Potential for High Impact:** Moderately high

Off-Label Scopolamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts:** Recent research implicates cholinergic pathways in both susceptibility to and symptoms of depression. This has created interest in anticholinergic drugs as possible antidepressant treatments. Scopolamine, a medication FDA previously approved for treating peptic ulcers, motion sickness, and post-surgical nausea, is a candidate anticholinergic drug with broad purported antidepressant properties. Researchers from Massachusetts General Hospital (Boston, MA) and the National Institute of Mental Health are conducting clinical trials investigating scopolamine for treating BPD and MDD.

In clinical trials, scopolamine has multiple administration protocols and routes: intravenous infusion, oral tablet, or transdermal patch formulations. Preliminary data from multiple trials suggests that scopolamine is rapid-acting as an antidepressant, and researchers have investigated its effectiveness in treating patients with treatment-resistant forms of BPD or MDD.

Scopolamine manufacturers do not appear to be pursuing expanded indications for scopolamine; thus, scopolamine could be prescribed off label for treating depression. Although intravenous scopolamine is most often used in clinical trials, only oral and transdermal patch formulations are available for retail purchase, with prices ranging from \$100 for a monthly supply of oral tablets to \$170 for 10 transdermal patches.

- **Key Expert Comments:** Overall, experts were somewhat optimistic about the potential of scopolamine to meet the need for rapid-onset, effective treatment for BPD and MDD. They acknowledged that scopolamine could affect multiple health system parameters, potentially lowering costs incurred from ineffective treatment, reducing suicide risk in patients requiring immediate intervention, and changing care settings from outpatient oral therapy to outpatient infusion therapy. Experts, however, noted the lack of definitive efficacy data from clinical trials and scopolamine's adverse event profile as barriers to adoption and diffusion.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Video Games for Cognitive Behavior Therapy for Adolescents with Major Depressive Disorder

- **Key Facts:** Nonpharmaceutical treatments for adolescents with early-onset major depressive disorder (eoMDD) may include supervised individual or group cognitive behavior therapy (CBT) sessions. These sessions are reportedly not appealing to many adolescents and have entrenched negative associations, resulting in limited patient engagement, reduced adherence to treatment, and failure to seek treatment. An unmet need exists for effective, outpatient, age-appropriate treatments for adolescent patients with eoMDD. Developed in New Zealand, SPARX™ is the first video game-based software intended for outpatient treatment of adolescents with eoMDD. The approach integrates traditional CBT concepts with an immersive, self-directed virtual environment modeled on popular role-playing “quest” games.

In published clinical trials, patients completing SPARX game modules reported significantly reduced depressive symptoms compared with patients receiving traditional in-person therapy sessions. SPARX patients reported high adherence rates with favorable perceptions of the software. Clinical trials are ongoing, and the software is being adapted for use with specialized patient subgroups.

SPARX has been licensed by LinkedWellness for commercial sale in North American markets. However, a free version of the software is available for download and use through two Web sites.

- **Key Expert Comments:** Overall, experts commenting on this intervention felt that it creatively and effectively addressed a significant unmet need for patients with eoMDD. Experts stated that SPARX could positively improve patient health outcomes without placing significant burden on health care delivery infrastructure, as the software can be used in private, outpatient environments with limited clinician oversight. As a video game-based intervention, SPARX could be widely adopted by patients and their guardians, experts thought. They also believe it has potential to reduce disparities in use and access that may accompany traditional behavioral therapy options for these patients. Although comments were generally positive, experts expressed a need for additional clinical trial data from patients outside New Zealand to demonstrate viability and efficacy, particularly considering pending commercialization in North America.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Depression and Other Mental Health Disorder Interventions

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Many patients with a diagnosis of bipolar depression (BPD) or major depressive disorder (MDD) do not respond well to available pharmacotherapies.¹ Existing medications also do not act rapidly to treat depressive symptoms, making the drugs ineffective for addressing acute episodes where immediate intervention is required to minimize severe risk of patient self-harm.^{1,2} Additionally, many common treatments for MDD and BPD have significant side effects that limit patient adherence.¹ An unmet need exists for fast-acting, well-tolerated, effective interventions for treating BPD or MDD. Ketamine, a widely used general anesthetic, may present an attractive off-label medication used at a low dose to treat this patient population.

Intervention: Ketamine is a racemic, noncompetitive, high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist that is approved by the U.S. Food and Drug Administration (FDA) for use as a general anesthetic.^{1,3} NMDA is a global receptor for glutamate, the major excitatory neurotransmitter, and also functions as a primary mechanism for controlling synaptic plasticity.^{1,4} Research has demonstrated that dysfunctional glutamate neurotransmission may underlie depressive symptoms BPD and MDD, although the exact mechanism of action has not been clarified.^{1,4,5} Because animal and in vitro models have shown that NMDA receptor signaling may mediate glutamate dysregulation, recent pharmacological studies have targeted NMDA receptor antagonists as novel treatments, hypothesizing that these antagonists may have antidepressant effects.^{5,6}

Preliminary data suggest that ketamine's antidepressant effects may result from its effects on synaptic plasticity and synaptogenesis, partly mediated by increased brain-derived neurotrophic factor (BDNF) levels.^{4,7-10} Other identified molecular targets of ketamine that may facilitate its antidepressant properties include mammalian target of rapamycin (mTOR) and eukaryotic elongation factor 2 kinase; both of these targets have demonstrated functions in synaptic plasticity.^{9,11-14} Recent animal model studies have also revealed that ketamine's antidepressant effects may be mediated by regulation of mitogen-activated protein kinase (MAPK) signaling pathways.

Although research has established an antidepressant role for ketamine's racemic form, the antidepressant activity of its individual R- and S-enantiomers has only recently been studied. Purified S-ketamine, also known as esketamine, is considered the more promising of the two for MDD and BPD, as it appears to underlie much of ketamine's NMDA receptor-antagonist properties, with limited side effects and significantly higher NMDA receptor-binding affinity and clinical potency.¹⁵

As monotherapy for MDD and BPD, ketamine is typically injected intravenously or intramuscularly at a low dose. Oral, intranasal, and rectal administrations have also been used and may represent viable alternate delivery routes for this indication, although bioavailability varies among formulations and administration routes.^{16,17} Ketamine has also been studied as an adjunct medication to electroconvulsive therapy (ECT) for treatment-resistant MDD. In many clinical trials investigating off-label ketamine for treating BPD or MDD, single, lower-than-anesthetic ketamine doses are used, and 0.5 mg/kg intravenous injections are the most frequently reported administrations.

Clinical trials: Multiple clinical trials are investigating off-label ketamine for treatment-resistant depression in both adolescents and adults with BPD or MDD.¹⁸⁻²³ Additional trials and case studies are also expanding into research on ketamine's treatment efficacy for suicidal ideation and as an adjunct treatment to behavior and brain-stimulation therapies.^{24,25} Completed studies have repeatedly reported positive, rapid, and long-lasting antidepressant effects of single intravenous

ketamine infusions in these patient populations, with the majority of results from patients with MDD.^{1,2,21,26} Results from studies using repeated ketamine doses have been less consistent, though, with reports suggesting that efficacy may vary across patients and depend on symptom severity and infusion protocols.²⁷⁻³⁰

In the largest reported randomized controlled trial (n=73) reported thus far, investigators at Baylor College of Medicine (Houston, TX) and the Icahn School of Medicine at Mount Sinai (New York, NY) examined the efficacy of single, intravenous ketamine doses compared with an active control, midazolam, for treating patients with treatment-resistant depression. After 24 hours, patients administered ketamine showed greater improvement in depression severity, by 7.95 points as measured by the Montgomery-Åsberg Depression Rating Scale (95% confidence interval, 3.20 to 12.71); the likelihood of response at 24 hours was also greater with ketamine infusions than with midazolam (64% versus 28%).¹⁸

For treating patients with BPD, intravenous ketamine was reported to produce significant improvements in depressive symptoms and suicidal ideations within 40 minutes compared with placebo. Investigators reported that 79% of patients (n=15) responded to ketamine.² A separate study (n=25) enrolling hospitalized adult patients with treatment-resistant BPD found that intravenous ketamine administration resulted in rapid and sustained improvements in depression severity (Hamilton Depression Rating Scale score: pre-infusion, 21±4; 6 hours after infusion, 19±6; 7 days after infusion, 12±7), and was well tolerated.²²

Comprehensive adverse-event reporting is not available from all of these clinical trials, but a recent systematic review on ketamine use in patients with MDD reported that treatment-related adverse events were generally mild, with some patients experiencing brief, reversible changes in blood pressure, heart rate, or respiratory rate.³¹ Individual case reports, however, have noted some severe adverse events, including delayed-onset suicidal ideation, dysphoria, and anxiety.³²

Ongoing trials, including two with the largest patient enrollments to date (100 and 324 patients) are investigating ketamine for treating MDD, BPD, and comorbid suicidal ideation.³³⁻³⁵ Trials are also investigating the efficacy of repeated ketamine administrations in treating depressive disorders, and trials are studying biomarkers that might predict patient response to ketamine for these indications. Two clinical trials, investigating optimal doses of intranasal esketamine for MDD and efficacy for treating depressed patients at high risk of suicide are also registered.^{36,37}

Manufacturer and regulatory status: Ketamine is available in generic form from several manufacturers, as well as in branded form, as Ketalar® (JHP Pharmaceuticals, LLC, Parsippany, NJ). FDA has approved ketamine for use as an anesthetic for diagnostic and surgical procedures; it is not labeled for treating BPD or MDD, and companies are not trial sponsors pursuing expanded labeling at this time. However, Janssen Research and Development (a subsidiary of Johnson and Johnson, New Brunswick, NJ) is developing intranasal esketamine for treating MDD and treatment-resistant MDD. FDA has granted fast-track status to esketamine for this indication, and Janssen has indicated plans to also apply for a breakthrough therapy designation.^{38,39} Janssen has completed multiple early-phase trials for these indications and has two new phase II trials registered.^{36,37}

Diffusion and costs: As a Schedule III controlled substance, ketamine cannot be purchased and administered without a U.S. Drug Enforcement Administration license.^{40,41} Groups including Columbia University (New York, NY), Massachusetts General Hospital (Boston, MA), the New York State Psychiatric Institute (New York, NY), and the National Institute of Mental Health (NIMH; Bethesda, MD) are sponsoring ketamine clinical trials for BPD and MDD.⁴²⁻⁴⁹ NIMH and Massachusetts General are primary collaborators of the two largest ongoing trials.^{34,49}

At higher doses, ketamine is sometimes abused as a street drug (“Special K”), which could affect attempts to expand approvals and availability for off-label use.^{50,51} Janssen has acknowledged

this issue and indicated it is evaluating methods to curtail abuse potential for its intranasal formulation.³⁸

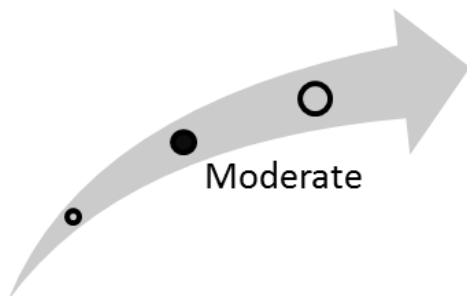
Some clinical practices report offering ketamine infusions for treating depression and the amount they charge; patient blogs also report patient experiences and out-of-pocket costs of ketamine infusions for MDD. Reported fees ranged from \$525 to \$1,250 per infusion; patients reported that an intranasal formulation was much less costly.⁵²⁻⁵⁵ A recent article in *Scientific American* reported off-label prescribing of ketamine for MDD has been increasing.⁵⁶

Clinical Pathway at Point of This Intervention

Available treatments for BPD and MDD include pharmacotherapies, group therapy, CBT, and other forms of individual psychotherapy. Antidepressant options for MDD include selective serotonin reuptake inhibitors, atypical antidepressants, and monoamine oxidase inhibitors as monotherapy and combination therapy.⁵⁷⁻⁵⁹ To treat BPD, lithium, anticonvulsant, antipsychotic, and benzodiazepine medications may also be used.⁶⁰ In treatment-resistant depression, physicians may also use ECT, forms of transcranial magnetic stimulation (TMS), or implanted vagus nerve stimulation.^{59,60}

Ketamine's mechanism of action and molecular targets differ from commonly used depression pharmacotherapies, leading to its potential to complement other approved medications. Some clinical researchers envision ketamine's rapid antidepressant action as a possible therapeutic bridge until standard antidepressants can take effect. Others are examining ketamine as an add-on to existing ECT, TMS, vagus nerve stimulation, and psychotherapy.

Figure 1. Overall high-impact potential: off-label ketamine for treatment-resistant bipolar depression and major depressive disorder



Experts commenting on this topic had favorable impressions of ketamine's potential as an effective, rapid-onset intervention for treatment-resistant BPD and MDD. If diffused, they predicted, ketamine may significantly affect health care delivery methods and patient management, while also affecting long-term patient health outcomes and health disparities. However, optimism for this intervention was tempered by the limited available clinical trial data, the administrative burdens required for ketamine use, and its known potential for abuse; ongoing clinical trials using intravenous ketamine, as well as investigations of oral and intranasal ketamine efficacy may address some of these concerns. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, patient safety, and health systems backgrounds, provided perspectives on off-label ketamine for this indication.⁶¹⁻⁶⁷ We have organized the following discussion of expert comments by the parameters on which experts commented; note that expert

comments are centered on analysis of intravenous ketamine infusions for treating BPD and MDD, as this specific intervention is better-developed than oral or intranasal ketamine administration for the same indication.

Unmet need and health outcomes: A moderate to significant unmet need exists for new options for treatment-resistant BPD and MDD, experts commented, citing a need especially for rapid-acting treatments. Experts' opinions varied regarding ketamine's potential health impact. Considering alternative, invasive treatments such as ECT, several experts anticipated that intravenous ketamine would have a moderate-to-large impact on health outcomes for these patients. However, lack of safety and efficacy data from recent clinical trials led other experts to predict that ketamine would have a small impact on health outcomes. Consensus indicated that data from larger, well-controlled clinical trials with sufficient followup are needed to accurately evaluate this intervention's impact on patient health outcomes.

Acceptance and adoption: Acceptance of this intervention among both clinicians and patients would be widespread, if data support its efficacy and safety, the experts thought. Several experts indicated that the lack of other effective medications for treatment-resistant MDD and BPD and the stigma associated with therapies such as ECT would drive adoption. Three experts with research backgrounds noted that, as a controlled substance with a publicized history of illegal abuse, ketamine might itself have stigmas that could hinder acceptance and adoption.^{63,65,66} An expert with a research and patient safety background also raised concerns that ketamine treatment protocols and intravenous administration may discourage adoption among patients accustomed to oral therapies.⁶⁶

Health care delivery infrastructure and patient management: Experts predicted that, compared with standard self-administered, oral antidepressant medications, intravenous ketamine treatment for these indications would result in minimal to moderate disruption of health care delivery infrastructure and patient management. Experts noted that patient management would be primarily changed by an increased need for patient monitoring after administration and physician interaction required for regular ketamine infusion or injection.

Health Disparities: The majority of experts thought that the availability of ketamine in an inexpensive generic form could help to minimize health disparities; however, patients' time and financial burdens incurred for regular intravenous ketamine administrations may adversely affect health disparities if health insurance does not cover the intervention. Conversely, one clinical expert explicitly noted the potential benefits of this intervention in addressing health for lower-socioeconomic patients who may have limited access to psychotherapy.⁶⁴

Off-Label Scopolamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Many cases of BPD and MDD are not effectively treated with available medications.¹ Existing treatments are also slow-acting, poorly tolerated, and ineffective for managing severe, acute depressive episodes.^{1,2} An unmet need exists for effective, fast-acting, and well-tolerated medications for treating BPD or MDD. If proven effective, scopolamine, a medication purported to exert rapid antidepressant activity, may address this need as a monotherapy or adjunct treatment.

Intervention: Scopolamine is a belladonna alkaloid that acts as a competitive inhibitor at muscarinic acetylcholine receptors (mAChRs) to exert potent anticholinergic properties.⁶⁸ Research has implicated the central nervous system–cholinergic system in the pathophysiology of depressive disorders. Patients with MDD or BPD may exhibit physiological signs of cholinergic hypersensitivity, including exaggerated neuroendocrine and pupillary responses and characteristic disturbances to normal REM (rapid eye movement) sleep cycles.⁶⁹ Also, certain genetic variations of mAChRs are associated with an increased risk of developing depression.⁷⁰

Although the mechanism of central nervous system cholinergic dysfunction in depression is not fully understood, some data suggest that increased cholinergic pathway activity contributes to the negative emotional-processing bias observed in many mood disorders.⁷¹ Researchers hypothesize that cholinergic hyperactivity can lead to overrepresentation of negative emotions, thereby promoting depression symptoms.⁷¹ Through inhibition of mAChRs, scopolamine purportedly counteracts cholinergic system hyperactivity in patients with depression. By inhibiting this cholinergic hyperactivity, it may be possible to restore normal emotional processing and alleviate depressive symptoms.⁷⁰ Clinical data suggest that these changes may be evident as soon as 3 days after treatment, providing a fast-acting alternative to standard antidepressants that can take several weeks to alleviate symptoms.^{72,73}

Clinical trials have investigated oral and intravenously administered scopolamine for treating depression. For intravenous administration, patients receive 4 mcg/kg, given during three sessions spaced 3–5 days apart.^{70,74} In a trial of orally administered scopolamine, a dosage of 0.5 mg twice daily, was used in conjunction with citalopram, an orally selective serotonin reuptake inhibitor.⁷³ Additionally, NIMH is sponsoring a clinical trial for this indication, investigating the antidepressant efficacy of a transdermal scopolamine patch.⁷⁵

Clinical trials: Relatively few recent completed clinical trials are available for this indication. In 2012, researchers reported data from a phase II/III trial (n=40) showing that patients receiving intravenous scopolamine as an adjunct to citalopram compared with placebo for treating MDD had increased rates of response (65% vs. 30%, p=0.027) and remission (65% vs. 20%, p=0.004).⁷³ Results from a separate clinical trial (n=52) with patients who had MDD or BPD suggested that intravenous scopolamine had significant, and gender-dependent, antidepressant efficacy, with larger treatment effect sizes observed among women than among men.⁷⁴

A 2013 systematic review supported the overall antidepressant efficacy of scopolamine across several routes of administration.⁷⁶ Additionally, preliminary data from a small patient subset (n=15) in the NIMH-sponsored trial demonstrated that scopolamine's antidepressant efficacy may be correlated with an functional magnetic resonance imaging activation in the bilateral middle occipital cortex region of the brain, indicating a potential neurological biomarker of patient response.^{71,75}

Safety information for either intravenous or transdermal scopolamine is limited for this indication. In the previously noted 2012 trial, investigators reported that patients administered intravenous scopolamine and citalopram had increased incidences of dry mouth, blurred vision, and dizziness compared with patients who were administered citalopram alone.⁷³ For scopolamine's

approved indications, additional commonly observed adverse events include pharyngitis, tachycardia, and urinary retention; less frequently observed severe adverse infusion-related events include confusion, agitation, hallucinations, paranoid behaviors, and delusions.^{68,77,78}

Clinical trials are ongoing for this off-label indication, including a large study (n=388) examining transdermal scopolamine.⁷⁵

Manufacturer and regulatory status: Oral scopolamine (methscopolamine bromide), in generic and branded forms, has FDA approval as an adjunct therapy for treating peptic ulcer disease. It is available from several manufacturers.^{78,79} Scopolamine is also available as an injection (scopolamine hydrobromide) and a transdermal, extended-release patch (Transderm Scōp; Novartis International AG, Basel, Switzerland). The injectable form is approved as a sedative and antiemetic, and the patch is indicated for treating motion sickness and postoperative nausea and vomiting.⁶⁸ Manufacturers of various scopolamine products do not appear to be pursuing expanded indications for treating MDD or BPD. Massachusetts General Hospital and NIMH are investigating off-label scopolamine for treating BPD and MDD. At Massachusetts General, two trials are testing intravenous scopolamine for treating MDD;^{33,80} NIMH is sponsoring a large trial examining the efficacy of the transdermal scopolamine patch for treating MDD.⁷⁵

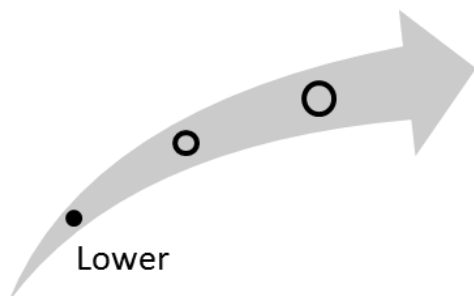
Diffusion and costs: Off-label scopolamine for treating MDD and BPD appears to be confined mainly to use in clinical trials at this time (unlike ketamine for MDD and BPD which appears to be available at many clinics outside the context of ongoing clinical trials). Oral and transdermal patch scopolamine formulations are available for purchase with a prescription; a monthly supply of methscopolamine tablets costs about \$100, while 10 3-day transdermal patches cost about \$170.^{81,82} Retail pricing information for intravenous scopolamine solution is not available.

Clinical Pathway at Point of This Intervention

Available treatments for BPD and MDD include pharmacotherapies, group therapy, CBT, and other forms of individual psychotherapy. Antidepressant options for MDD include selective serotonin reuptake inhibitors, atypical antidepressants, and monoamine oxidase inhibitors as monotherapy and combination therapy.⁵⁷⁻⁵⁹ To treat BPD, lithium, anticonvulsant, antipsychotic, and benzodiazepine medications may also be used.⁶⁰ In treatment-resistant depression, physicians may also use ECT, forms of TMS, or implanted vagus nerve stimulation.^{59,60}

Scopolamine's mechanism of action differentiates it from standard medications for treating depression. As such, it could complement other pharmacotherapies, in combinations such as scopolamine and citalopram. If its rapid onset of action is sustained, scopolamine could also serve as a therapeutic bridge until standard antidepressants take effect. Scopolamine could also complement nonpharmacologic interventions such as TMS, ECT, vagus nerve stimulation, and psychotherapy.

Figure 2. Overall high-impact potential: off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder



Expert commenting on this topic expressed limited optimism regarding scopolamine's potential to function as a rapid-onset, effective treatment for patients with treatment-resistant BPD and MDD. If validated, they stated, scopolamine could affect health care delivery infrastructure, shifting care from self-administered oral medication to infusion therapy administered in clinical settings. Support for this intervention was restrained, however, because of this intravenous administration route, as well as the risk of anticholinergic effects noted for scopolamine's approved indications. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, commented on off-label scopolamine for this indication.⁸³⁻⁸⁸ We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Although experts commenting on this intervention acknowledged the importance of the unmet need for effective treatment for patients with treatment-resistant BPD and MDD, several expressed a need for additional safety and efficacy data from clinical trials, to confirm that scopolamine could address this need. Overall, the majority of experts considered the preliminary data for this indication to sufficiently support efficacy in treating these indications and anticipated a moderate impact on patient health outcomes. Two experts with health research backgrounds, however, anticipated a small impact on health outcomes, citing the short followup times of the studies and lack of consistent administration protocols across clinical trials.^{85,88}

Acceptance and adoption: For this indication, experts anticipated moderate to widespread acceptance and adoption of scopolamine by both patients and clinicians. However, two clinical experts remarked that scopolamine's side effects and potential contraindications for anticholinergic medication could limit adoption and cautioned that appropriate patient screening would be required.^{86,87} An expert with a research background also noted that, if administered intravenously, scopolamine may be more slowly adopted by patients.⁸⁸

Health care delivery infrastructure and patient management: Generally, experts expected that oral and transdermal scopolamine use would cause little to no disruption to health care delivery infrastructure and patient management, with both formulations likely employed as adjunct treatments added to existing therapies. However, several experts stated that intravenous scopolamine administration could be significantly more disruptive; one health systems expert anticipated that this formulation may eventually be provided only as an inpatient therapy.⁸⁷ A second clinical expert noted that scopolamine use could actually reduce the need for inpatient stays or costly alternative treatments.⁸⁶

Health Disparities: Several experts noted that the impact of scopolamine on health disparities was dependent upon the available/required route of administration and subsequent accessibility of the treatment. Most experts did not expect this intervention to produce a large impact on disparate populations, but noted that cost could be a factor, with generic scopolamine formulations potentially reducing disparities.

Video Game for Cognitive Behavior Therapy for Adolescents with Major Depressive Disorder

Unmet need: Despite the high incidence of early-onset major depressive disorder (eoMDD) among adolescents and the demonstrated effectiveness of CBT for patients with mild to moderate eoMDD, many affected patients fail to seek or receive treatment. Research suggests that even among adolescents who identify themselves as needing mental health intervention, up to 85% do not use available services.⁸⁹⁻⁹¹ An unmet need exists for effective, engaging treatments for this patient population. SPARX, a self-directed computerized CBT (cCBT) program, may directly address this need, providing a treatment option that increases ease of access and overcomes the stigma commonly associated with traditional treatments.

Intervention: Seven modules comprise the SPARX (Smart, Positive, Active, Realistic, X-factor) thoughts-depression-intervention software. The game is self-directed cCBT intended primarily for use by adolescents with eoMDD. Each module is based in a virtual, fantasy world, video game environment. The game is designed to teach and reinforce cCBT techniques for identifying and addressing negative thoughts and feelings and using appropriate coping strategies.

Within the game, patients select an in-game avatar, used to interact with other virtual characters, including a “guide” avatar who introduces and reviews cCBT techniques at the start and finish of each module. Guide avatars also regularly engage the patient to gauge his or her mood and advise those who are not improving to seek additional intervention from referring clinicians or therapists. Modules are about 30 minutes long, and patients are instructed to complete 1–2 modules weekly. Full module completion is expected to take between 4 and 7 weeks.⁹² A notebook is provided as a supplement to the software, giving patients an additional space to write feedback notes and questions regarding their mood and progress throughout the modules. Clinicians also monitor patients’ progress through the modules via an online monitoring system or in person.⁹³

As a self-directed cCBT program, SPARX software purportedly provides both an alternate treatment option for patients with eoMDD already receiving treatment and a primary treatment option for patients who otherwise would not pursue treatment. The developers expect SPARX to be used in patient’s homes; in schools, possibly with oversight from a trained counselor or clinician; and in clinician offices as an adjunct to standard psychotherapy.

Clinical trials: Preliminary and late-phase clinical trials use Child Depression Rating Scale (CDRS) scores as primary assessment tools to measure program efficacy. In two preliminary trials (n=32 and n=34), adolescent patients with MDD were randomly assigned to complete the SPARX computer modules or to receive standard, in-person behavior therapy. Investigators reported high patient adherence (81% and 94%; adherence defined as patients completing at least 4 of 7 modules in the first trial and completing all modules in second trial) and favorable patient-evaluated program ratings in both trials. Additionally, in both trials, patients completing SPARX demonstrated significantly greater symptom improvement compared with symptoms in patients who received behavioral therapy.^{94,95}

In a large clinical trial (n=187), adolescent patients who were already seeking help for depressive symptoms were randomly assigned to complete SPARX or standard in-person behavioral therapy. Patients completing SPARX showed larger mean reductions in CDRS scores (10.32 vs. 7.59, p=0.079) and significantly higher remission (43.7% vs. 26.4%, p=0.030) than patients receiving standard behavioral therapy.⁹³

The program developers recently evaluated a customized version of SPARX, designed for adolescent patients with depressive symptoms who also identify as members of sexual minority groups (i.e., adolescents sexually attracted to the same sex, both sexes, or who are questioning their

sexuality). Preliminary feasibility and efficacy data for this intervention were reported in April 2014, demonstrating significant decreases in depressive symptoms among patients after completing the seven-module program ($p < 0.0001$; effect size $d = 1.01$), with decreases maintained at a 3-month follow-up.⁹⁶

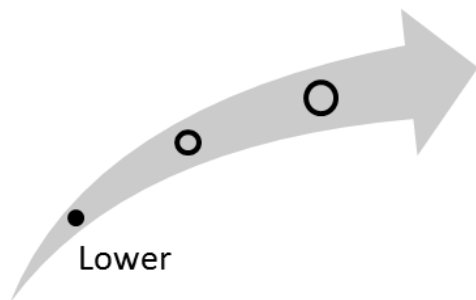
Three ongoing clinical trials are investigating SPARX's efficacy for treating depression in adolescent patients in New Zealand and the Netherlands.

Manufacturer and regulatory status: SPARX software was originally developed by researchers at the University of Auckland (Auckland, New Zealand) Department of Psychological Medicine, led by Dr. Susan Merry. LinkedWellness (Baltimore, MD) holds an exclusive license from Auckland UniServices, Ltd., the commercialization company of the university, to commercialize SPARX in North America.⁹⁷ The original version is accessible for free online at Web sites hosted by the University of Auckland and LinkedWellness. New software versions, including specific modules designed for adolescents with antisocial comorbidities and sexual minority youth are being developed and used in clinical trials.^{93,96}

Clinical Pathway at Point of This Intervention

After an adolescent patient presents with symptoms indicative of MDD, physical and psychological examinations are conducted to establish a definitive diagnosis of eoMDD. Patients with a confirmed diagnosis are typically prescribed antidepressants, some type of behavioral therapy, or combination therapy. CBT with SPARX software would be used as an outpatient intervention with regular clinician monitoring. It could be prescribed as a monotherapy, replacing medication, traditional talk or behavior therapy, or as an adjunct to these treatments.⁹³

Figure 3. Overall high-impact potential: video game for cognitive behavior therapy for adolescents with major depressive disorder



Overall, experts commenting on this topic were optimistic about its potential to address the need for an effective, well-tolerated treatment for eoMDD. Experts were impressed by the software's ability to present accepted behavior therapy concepts in an engaging format and predicted broad acceptance by patients who might view other eoMDD treatments unfavorably. Although experts remarked that SPARX's initial clinical trial data were promising, they noted a need for additional efficacy data, particularly from adolescents outside of New Zealand, because the software will be sold in other countries whose adolescents may have different cultural backgrounds and needs. Experts also stated that, as a computer-based intervention requiring minimal oversight, SPARX will not significantly add to health care delivery infrastructure or patient management burdens and would be welcomed by many clinicians. However, as an intervention that has not been demonstrated to prevent eoMDD, SPARX has only moderate ability to improve patient health outcomes. Based on this input, our overall assessment is that this intervention is at the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.⁹⁸⁻¹⁰³ We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Experts acknowledged that eoMDD represents an important and growing health issue and agreed that SPARX could address an unmet need for new therapy options for this indication. Citing poor patient adherence and acceptance as shortcomings of available treatments, experts remarked that SPARX could positively affect patient health outcomes by providing an alternative for patients already receiving eoMDD treatments and thought it could increase the number of untreated patients who engage in treatment.

Acceptance and adoption: Potential clinician acceptance and adoption would be moderate, experts evaluating SPARX thought, stating that this intervention is primarily patient-directed, and additional clinical trial data are desired to promote broad acceptance among providers accustomed to standard treatments. An expert with a research background also noted that individual clinicians' acceptance might be contingent on whether they view this intervention as a potential monotherapy or as an adjunct to standard care.⁹⁹

Conversely, experts anticipated wide acceptance and high adoption among patients, who may view SPARX as an engaging, entertaining treatment option that does not carry the stigma or side effects of standard treatments. After viewing online demos for this intervention, one expert with a health systems background favorably compared it to commercial video games, predicting that patients would be particularly amenable to SPARX as a treatment.¹⁰¹

Health care delivery infrastructure and patient management: Noting that SPARX is a computer-based intervention, experts agreed that it would pose little to no additional burden to health care delivery infrastructure and patient management. Experts also noted that treatment settings may shift from clinician offices and behavior-therapy facilities to patient's homes or schools.

Health Disparities: Overall, experts predicted that SPARX would have minimal impact on health disparities, but were divided in their rationales. Some experts noted that making eoMDD treatment available to any patient with computer access could reduce disparities. However, other experts observed that the software is available only in English, potentially limiting access by non-English speakers. Additionally, some experts noted that although a free version is available online, if fully commercialized, this intervention may not be affordable to patients of lower financial means or patients who have no routine Internet access.

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